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Metastatic neuroendocrine carcinoma presenting with left lateral rectus enlargement and orbital cellulitis

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ABSTRACT

Neuroendocrine tumors (NETs) of the orbit are a rare but increasingly recognized clinical phenomenon. The vast majority of orbital NETs are metastatic, and most metastasize from the gastrointestinal system to the extraocular muscles. While orbital metastasis typically occurs in the setting of a known primary neoplasm, some cases represent the initial manifestation of disease and can precede detection of the primary tumor by many months. We report a 58-year-old woman who presented with diplopia, unilateral orbital pain, erythema, and chemosis as the primary presentation of a metastatic small intestine NET. This case serves as a reminder that identification of orbital NETs should prompt investigation for primary gastrointestinal or pulmonary NETs. Goals of surgery include obtaining a tissue sample, debulking the lesion, and preserving visual function.

KEYWORDS Midgut; neuroendocrine tumor; orbital metastasisneuroendocrine tumor

Neuroendocrine tumors (NET), previously known as carcinoid tumors, derive from the neuroendocrine system.[1] They typically originate from the gastrointestinal or pulmonary systems and have a propensity to metastasize to the orbit, specifically the extraocular muscles.[2] A 2020 review of 94 cases of orbital NETs, the largest to date, found that 88 of 94 (94%) of NET orbital tumors were metastatic, with most metastases (52 of 88 cases, 59%) coming from the gastrointestinal system.[3] Studies have shown excellent absolute 5-year survival rates for NET orbital metastasis of 70% to 80%,[3–5] although patients with disease localized to the orbit at presentation live longer than those with disseminated disease.[4] In this article, we describe a patient who presented with periorbital pain, diplopia, and eyelid erythema and was found to have a unilateral NET in her lateral rectus muscle as the initial manifestation of her metastatic small intestine NET.

CASE DESCRIPTION

A 58-year-old white woman presented with 2 weeks of left periorbital pain, erythema, and diplopia worsened with abduction. She denied fever and weight loss. She had no personal medical history, had never smoked, and had received all age-appropriate cancer screening. External examination revealed left periorbital edema, erythema, 2 mm of proptosis, and hemorrhagic chemosis of the left conjunctiva *(Figure 1a)*. Visual acuity was 20/30 in both eyes. The left pupil was 5 mm and nonreactive to light or accommodation, and the right pupil was 3 mm and reactive to light and accommodation, suggesting an afferent pupillary defect and third nerve palsy. There was reduced abduction of the left eye. Visual fields were full bilaterally. Slit lamp and funduscopic examinations were unremarkable. Magnetic resonance imaging (MRI) of the orbits with and without intravenous contrast showed a 3.7 cm^3, fusiform, centrally necrotic, hyperintense on T2 lesion within the lateral rectus with surrounding edema *(Figure 1b)*.

The patient underwent transconjunctival left orbitotomy with incisional biopsy and debulking of the lateral rectus lesion. Histopathologic analysis showed well-differentiated NET with uniform cells and regular nuclei with expression of neuroendocrine markers including chromogranin A and synaptophysin. Immunostaining revealed expression of CDX2 and villin, found in small intestine primary tumors *(Figure 2)*. The Ki-67 proliferative index was low. Subsequent staging computed tomography (CT) revealed a 10 mm enhancing nodule in the small bowel mesentery. A

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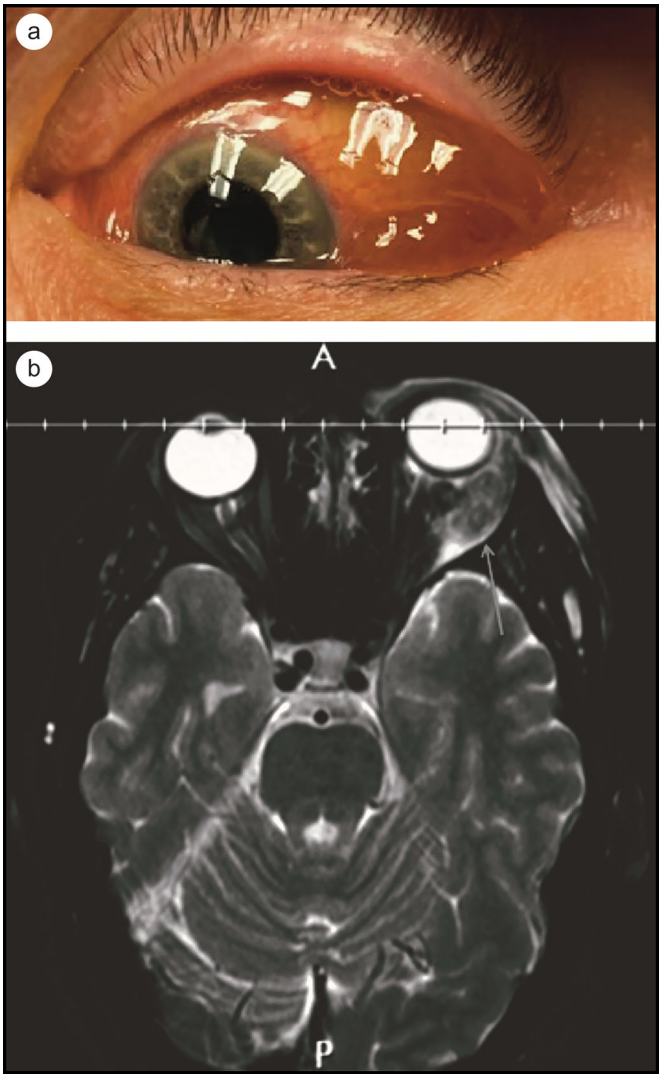

Figure 1. **(a)** Hemorrhagic chemosis of the left lateral conjunctiva and sclera. **(b)** T2-weighted postcontrast MRI showing a left lateral rectus lesion with central necrosis (arrow).

^{68}Ga-DOTATATE scan revealed the focus of activity within the lateral aspect of the left orbit, the distal ileum, and an ileocolic mesenteric lymph node. Somatostatin receptor scintigraphy demonstrated no somatostatin-receptor positivity. At 2-month follow-up, the patient's headache, diplopia, and afferent pupillary defect had resolved. Given the low volume of residual disease, further surgical debulking and systemic therapies were deferred.

DISCUSSION

The usual mechanism of NET orbital metastasis is hematogenous spread from the gastrointestinal and pulmonary tracts.[3,6] Proposed theories to explain the predisposition of NETs for orbit metastasis include immunologic mechanisms and tumor cell adhesion factors in the local cellular microenvironment.[7] Midgut primary NETs typically metastasize to the extraocular muscles, whereas primary bronchial tree NETs metastasize to the uveal tract.[8]

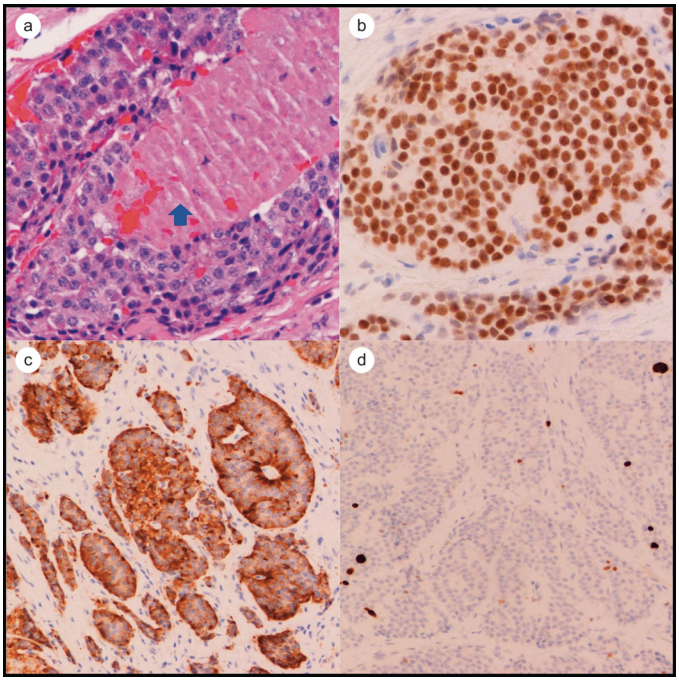

Figure 2. **(a)** Malignant epithelial cells with single uniform round to oval nucleus with inconspicuous nucleoli and modest amounts of pale eosinophilic cytoplasm arranged in solid nests and sheets. The blue arrow shows tumor necrosis. **(b)** Positive immunostaining for CDx2. **(c)** Positive immunostaining for synaptophysin. **(d)** Ki-67 stain with a low proliferative index.

Metastasis to the orbit usually occurs in the setting of a known NET. In the previously mentioned review by Hatsis et al, orbital metastasis was detected following detection of a primary tumor in 73 of 94 (78%) cases, with a median time to metastasis of 36 months (range 0-288 months). In 15 of 94 cases (16%), ocular symptoms from orbital metastasis were the primary presentation of disease.[3] The most commonly reported symptoms are proptosis, diplopia, and decreased visual acuity.[6]

MRI remains the gold standard for imaging orbital metastasis. Suggestive features include well-defined, round, or fusiform masses that are hyperintense on T2-weighted imaging.[9] In 2016, the Food and Drug Administration approved the ^{68}Ga-DOTATATE positron emission tomography (PET)/CT, which utilizes radioisotopes and PET tracers to localize NETs.[10] Somatostatin receptor scintigraphy is also useful, as it can help determine candidacy for somatostatin analog therapy and peptide receptor radiotherapy,[11] which are adjunct therapies in NETs.

Histopathological diagnosis of NETs with immunostaining allows for evaluation of tumor differentiation and grade.[11] Surgical treatment and tumor debulking with or without adjuvant chemotherapy, radiotherapy, or biologics remain the mainstay of management for symptomatic orbital tumors.[3] The location of the tumor, size of the lesion, and goal of surgery (e.g., biopsy, debulking, or gross total excision) should be considered when selecting an approach to NET orbital metastasis cases. Complications of surgery

include visual deterioration and residual disease.[12] Chemotherapy and radiation treatments may be sufficient to manage early or limited disease,[9] but recent studies of patients with NET tumors found that patients treated with systemic chemotherapy had a shorter survival time than patients not treated with systemic chemotherapy; further, there was no survival benefit to surgical, radiation, or octreotide therapies.[4]

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Avocations

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